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Review Article

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Recent Advances in Systemic Therapy for Advanced Intrahepatic Cholangiocarcinoma

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Abstract
Background: The incidence of intrahepatic cholangiocarcinoma (IHCCA) is rising around the world. The disease is becoming a major global health issue. Conventionally, most patients with cholangiocarcinoma present with advanced disease and systemic therapy is the mainstay of treatment. This review discusses recent advances in systemic treatments for patients with IHCCA. ***Summary:*** The addition of durvalumab to a gemcitabine plus cisplatin regimen has significantly improved overall survival in the phase 3 TOPAZ-1 trial and is currently recommended as a standard first-line treatment. The phase 3 ABC-06 and phase 2b NIFTY trials have shown the benefit of second-line fluoropyrimidine plus oxaliplatin, and fluoropyrimidine plus nanoliposomal irinotecan, respectively. They have provided a treatment option for patients without actionable alterations who progressed to first-line therapy. For patients with actionable genomic alterations, including *FGFR2* rearrangement, *IDH1* mutation, *BRAF* mutation, and *ERBB2* amplification, targeted agents have shown encouraging efficacy in several phase 2–3 trials, and are recommended as subsequent treatments. Immune checkpoint inhibitors are being investigated for the treatment of previously treated patients, although only a small proportion of patients showed durable responses. ***Key Messages:*** Recent advances in systemic treatments have improved clinical outcomes in patients with advanced IHCCA. However, most patients eventually show resistance to the treatment, and tumor progression occurs within a year. Indeed, there should be further efforts to improve the outcomes of patients with advanced IHCCA.

Introduction

Biliary tract cancer (BTC) is a group of epithelial malignancies arising from the biliary tree and gallbladder. It shows heterogeneous biology and clinical behaviors are according to the location of the primary tumor [1]. Cholangiocarcinoma refers to BTC which originates from the intrahepatic and extrahepatic bile duct. Following hepatocellular carcinoma, it is the second most

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common primary cancer of the liver [2]. The incidence of cholangiocarcinoma differs around the world with a higher incidence in endemic regions, including East Asia and Thailand [1–4]. The incidence of cholangiocarcinoma has recently begun to increase, and especially the incidence of intrahepatic cholangiocarcinoma (IHCCA) is rising in developed countries, including the USA and UK [1, 3, 5–7]. Because cholangiocarcinoma usually presents asymptomatically at the early stage, most patients are diagnosed at advanced stages and have poor prognoses [2]. In recent years, many new treatment options, including targeted agents and immunotherapies, have shown encouraging results with improvements in the outcomes of patients with unresectable BTC, including IHCCA. This review discusses recent advances in systemic treatments for patients with IHCCA.

Cytotoxic Chemotherapy

First-Line Doublet Therapy

Standard first-line cytotoxic chemotherapy was established based on the results of the ABC-02 trial presented in 2010. This landmark phase 3 study provided the evidence for use of gemcitabine plus cisplatin (GemCis) in BTC. The ABC-02 trial randomized 410 patients with locally advanced unresectable or metastatic BTC to GemCis or gemcitabine monotherapy. Study treatment was given for up to 24 weeks, and response evaluation was performed every 12 weeks. In this study, median overall survival (OS) was significantly improved with GemCis over gemcitabine monotherapy (11.7 vs. 8.1 months, hazard ratio [HR] = 0.64 [95% CI = 0.52–0.80], $p < 0.001$) [8]. The median progression-free survival (PFS) in the GemCis and gemcitabine monotherapy groups was 8.0 versus 5.0 months, HR = 0.63 (95% CI = 0.51–0.77, $p < 0.001$). The clinical benefit of adding cisplatin in terms of OS was consistent across different primary tumor types (i.e., IHCCA, extrahepatic cholangiocarcinoma [EHCCA], and gallbladder carcinoma [GBCA]). Although the objective response rate (ORR) was not specified according to primary tumor type, GemCis showed 18% of ORR in patients with IHCCA, EHCCA, and ampullary cancer. A subsequent Japanese phase 2 BT22 randomized trial confirmed that adding cisplatin to gemcitabine is beneficial to advanced BTC patients ($n = 83$) in the Asian population. The median OS was 11.2 months in the GemCis group and 7.7 months in the gemcitabine monotherapy group (HR = 0.69, 95% CI = 0.42–1.13) [9]. The median PFS in the GemCis and gemcitabine monotherapy groups was 5.8 versus 3.7 months (HR = 0.66, 95% CI = 0.41–1.05). From an individual patient data meta-analysis of the two trials, GemCis demonstrated significant improvement in OS outcomes compared to gemcitabine alone (HR = 0.65, 95% CI = 0.54–0.78) regardless of ethnicity and primary tumor, although patients with poor performance (Eastern Cooperative Oncology Group performance status 2) and ampullary cancer did not show survival benefit with addition of cisplatin [10].

The efficacy and safety of GemCis in advanced BTC were validated in a large retrospective study, including 740 patients. In this study, real-world median PFS and OS were 5.2 and 10.4 months, respectively [11]. Although there was no randomized trial comparing the efficacy and safety of oxaliplatin in combination with gemcitabine (GEMOX) with GemCis, GEMOX was preferred as a daily practice regimen in some geographic regions and was used as reference regimens in several phase 2 and 3 trials for BTC [12]. However, there is currently insufficient evidence to recommend GEMOX as preferred first-line treatment option.

Fluoropyrimidine-based first-line therapy has also been investigated. In a randomized phase 3 trial including 114 patients with advanced BTC, capecitabine plus oxaliplatin showed a non-inferiority to GEMOX as first-line therapy. Regarding PFS, the median was 5.3 versus 5.8 months, respectively, and OS was 10.4 versus 10.6 months, respectively [13]. There was an attempt to develop the non-platinum-based first-line therapy for BTC in Japan. In the FUGA-BT (JCOG1113), S-1 – an oral fluoropyrimidine that is widely used for the management of gastric cancer in Asia – was combined with gemcitabine and compared with GemCis [14]. In this non-inferior phase 3 trial including 354 patients, S-1 plus gemcitabine showed non-inferiority to GemCis in terms of OS (median: 15.1 vs. 13.4 months) and PFS (6.8 vs. 5.8 months) [14].

First-Line Triplet Therapy

Triplet cytotoxic chemotherapy regimens have been investigated to improve the efficacy outcomes of GemCis doublet. In a phase 3 trial performed in Japan, the addition of S-1 to GemCis has shown improvement in OS outcomes with HR of 0.79 (90% CI: 0.628–0.996), although it was less than assumed benefit (HR: 0.71) and improvement in median OS was minimal (13.5 vs. 12.6 months) [15]. Based on the success of FOLFIRINOX in pancreatic adenocarcinoma, the PRODIGE 38 AMEBICA trial, an open-label randomized phase 2–3 study comparing modified FOLFIRINOX and GemCis in patients with advanced BTC, was performed [16]. In this study, which was designed to show the superiority of

modified FOLFIRINOX to GemCis, a total of 185 patients were included in the modified intention-to-treat population, and the 6-month PFS rate, primary endpoint, was 44.6% in the modified FOLFIRINOX arm and 47.3% in the GemCis arm. This study was stopped after phase 2 because of its failure to meet the primary study endpoint [16]. GemCis in combination with nab-paclitaxel was investigated in a single-arm phase 2 trial [17]. Initially, this triplet regimen consisted of gemcitabine 1,000 mg/m^2, cisplatin 25 mg/m^2, and nab-paclitaxel 125 mg/m^2, but because of a high incidence of grade 3/4 hematological adverse events in the first 32 patients, the doses were reduced to 800, 25, and 100 mg/m^2, respectively. In this study, ORR was 45% and the disease control rate was 84%. Survival outcomes were encouraging with median PFS and OS of 11.8 months and 19.2 months, respectively. However, in the phase 3 SWOG 1815 trial recently reported at the 2023 ASCO GI Cancer Symposium, addition of nab-paclitaxel to GemCis did not improve OS outcomes (HR: 0.93, median OS: 14.0 vs. 12.7 months, $p = 0.58$) with significantly higher grade ≥3 hematologic adverse event (60% vs. 45%, $p = 0.003$) [18].

Second-Line Therapy

For more than a decade, there was no globally recognized standard of care for the management of advanced BTC that progressed on GemCis. However, these patients have been widely managed with fluorouracil (5-FU)-based regimens in clinical practice, despite the absence of high-level evidence based on randomized trials to support the use of these regimens and their modest efficacy [19, 20]. In one of the largest retrospective studies that included 321 patients who progressed on first-line GemCis, fluoropyrimidine monotherapy or fluoropyrimidine-platinum combination showed an ORR of 3% and a disease control rate of 47%. The median PFS and OS were 1.9 months and 6.5 months, respectively. There were no significant differences in terms of PFS ($p = 0.43$) and OS ($p = 0.88$) between fluoropyrimidine monotherapy and fluoropyrimidine-platinum combination [21].

Meanwhile, the ABC-06 trial showed a significant increase in OS with active symptom control (ASC) plus fluorouracil and leucovorin plus oxaliplatin (FOLFOX) compared with ASC alone in patients with advanced BTC who had previously been treated with GemCis [22]. The ABC-06 trial was the first randomized study to show the benefit of second-line chemotherapy in patients with advanced BTC. A total of 162 patients were enrolled in this open-label phase 3 study conducted in the UK. The median OS, the primary endpoint, was significantly longer in the ASC plus FOLFOX group than in the ASC alone group, with a median of 6.2 months in the ASC plus FOLFOX group versus 5.3 months in the ASC alone group (adjusted HR = 0.69, $p = 0.031$). The median PFS was 4.0 months, and ORR was 4% in the ASC plus FOLFOX group. Radiological tumor evaluation was performed 12-weekly in the ABC-06 trial.

The NIFTY trial is a Korean multicenter, open-label, randomized phase 2b trial that investigated the use of nanoliposomal irinotecan (nal-IRI) plus 5-FU/leucovorin (LV), which is a standard subsequent treatment after progression on gemcitabine-based chemotherapy in pancreatic adenocarcinoma, as second-line therapy in patients with advanced BTC who progressed on first-line GemCis [23]. In this large randomized trial ($n = 174$ patients), nal-IRI plus 5-FU/LV was compared to 5-FU/LV. The primary endpoint of this study was blinded independent central review (BICR)-assessed PFS. BICR and tumor evaluations were performed 6-weekly on a fixed schedule. Nal-IRI plus 5-FU/LV demonstrated significant improvement regarding PFS and OS compared to 5-FU, as median BICR-assessed PFS was 7.1 months in the nal-IRI plus 5-FU/LV arm and 1.4 months in the 5-FU/LV arm (HR = 0.56, $p = 0.0019$), median investigator-assessed PFS was 3.9 and 1.6 months, respectively (HR = 0.48, $p < 0.001$), and median OS was 8.6 and 5.5 months, respectively (HR = 0.68, $p = 0.035$). With extended follow-up of 1.3 years, the significant improvement in survival outcomes with nal-IRI plus 5-FU/LV compared to 5-FU/LV alone was maintained [24, 25]. Also, BICR was re-performed with three newly invited radiologists considering relatively high discrepancy rate between BICR and investigator-assessed progression date, and with reduced discrepancy rate (30–17.8%), nal-IRI plus 5-FU/LV showed significant improvement in BICR-assessed PFS compared to 5-FU/LV alone (median: 4.2 vs. 1.7 months, HR: 0.61, $p = 0.004$) [24, 25]. However, from the phase 2 NALIRICC trial performed in Germany, nal-IRI plus 5-FU/LV did not show survival benefit compared to 5-FU/LV alone [26]. Difference in sample size (174 patients in the NIFTY trial vs. 100 patients in the NALIRICC trial) and proportion of patients with IHCCA (64% vs. 43%) may be attributable to the discrepancy in the results of the two trials, and difference in ethnicity (Asian vs. white) may also be the reason [26]. Asian patients showed differences in pharmacokinetic profiles of nal-IRI, and this may be associated with higher incidence of grade 3/4 diarrhea among patients who received nal-IRI in the NALIRICC trial compared to the NIFTY trial (15% vs. 5%) [26, 27]. Consequently, this may also explain the lack of improvement in survival

outcomes in the nal-IRI plus 5-FU/LV group compared to 5-FU/LV alone group in the NALIRICC trial, despite higher ORR (14.3% vs. 3.9%) [26]. Additionally, exploratory analysis of the phase 3 NAPOLI trial for patients with pancreatic cancer showed longer OS in Asian patients treated with nal-IRI plus 5-FU/LV [28]. Based on the results of the phase 3 ABC-06 trial and phase 2b NIFTY trial, FOLFOX and nal-IRI plus 5-FU/LV are recommended as second-line therapy after progression on first-line GemCis in patients who do not have targetable genetic alterations, respectively.

The role of conventional irinotecan in advanced BTC remains unclear. In a recent Korean randomized phase 2 study that included 118 patients who progressed on first-line GemCis, there were no statistical differences between modified FOLFIRI and modified FOLFOX in terms of ORR (4.0% vs. 5.9%, respectively), PFS (2.1 vs. 2.8 months, respectively), and OS (5.7 months vs. 6.3 months, respectively) [29]. This trial was originally designed to show the superiority of modified FOLFIRI over modified FOLFOX, and the sample size was insufficient to show non-inferiority of modified FOLFIRI to modified FOLFOX. Furthermore, clinical outcomes of modified FOLFIRI in this study were numerically inferior to those shown with nal-IRI plus 5-FU/LV in the NIFTY trial. Future trials should further validate the role of conventional irinotecan. Table 1 summarizes the prospective clinical trial results of cytotoxic agents for patients with advanced BTC.

Targeted Therapy

Genomic Landscape of Cholangiocarcinoma

Although several studies have shown the molecular heterogeneity of IHCCA, EHCCA, and GBCA, there are several common genomic alterations in each subtype of BTC [1, 48]. Isocitrate dehydrogenase-1 (*IDH1*) mutation and rearrangement of the fibroblast growth factor receptor (*FGFR*) 2 gene are almost exclusively found in IHCCA, while mutations of *KRAS* and *TP53* and *ERBB2* amplifications are more commonly found among patients with EHCCA [1, 49–52]. Alterations in *BAP1*, *BRAF*, *ARID1A*, *CDK2NA*, and *MET* genes are also frequently found in IHCCA, while EHCCA shows frequent alterations in *SMAD4*, *ERBB3*, and *ELF3* genes and fusions of *PRKACA* and *PRKACB* [2, 48, 53]. Interestingly, the patterns of genomic alterations in IHCCA can be differentiated according to the size of the originating bile duct, which reflects the putative cell of origin [2]. While IHCCA arising from small bile ducts or bile ductules has frequent mutations in *IDH1* and *FGFR2* rearrangement, IHCCA arising from large bile ducts has an increased frequency of alterations in *KRAS* and *TP53* as in EHCCA [2, 33, 54–58].

Because several of the frequently found alterations are targetable, genomic profiling of patients with advanced IHCCA is essential for providing optimal treatment options. From a molecular profiling analysis of patients with cholangiocarcinoma using the MSK-IMPACT platform, 93 of 195 patients (47.6%) involved had at least one actionable alterations with 3B or higher according to OncoKB classification [57]; 26.9% (n = 25) of them received matched therapy, including IDH1 inhibitor, FGFR inhibitor, EZH2 inhibitor, ERK inhibitor, and HER2-directed therapy. Sixteen patients (66%) among 25 patients treated with matched targeted agents showed clinical evidence of response to the treatment [57].

Targeted Agents

FGFR2 Rearrangement

From a recent molecular analysis including huge population of IHCCA (n = 6,130), rearrangement of the *FGFR2* gene was found in 576 patients (9.4%) [59]. Several nonselective FGFR inhibitors have shown efficacy against IHCCA with *FGFR2* gene rearrangement, including pemigatinib, infigratinib, and futibatinib [34]. From the FIGHT-202 multicenter single-arm phase 2 trial of previously treated patients with advanced cholangiocarcinoma, 107 patients with FGFR2 rearrangement who received pemigatinib, a nonselective FGFR inhibitor, showed ORR of 35.5%, and median PFS and OS of 6.9 months (95% CI = 6.2–9.6) and 21.1 months (95% CI = 14.8–NR), respectively [60]. From the final analysis, median PFS and OS were 7.0 months (95% CI = 6.1–10.5) and 17.5 months (95% CI = 14.4–22.9), respectively [61]. Interestingly, from a post hoc analysis of the trial, patients with objective response to the treatment (responders) showed significantly longer OS outcomes compared to the nonresponders (median OS: 30.1 months vs. 13.7 months) [62]. Pemigatinib has received accelerated approval by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the National Institute for Health and Care Excellence for the subsequent treatment of patients with *FGFR2* rearrangement-positive IHCCA, and further phase 3 confirmative trial is required.

In the FIGHT-202 trial, the most observed adverse events were hyperphosphatemia, which was shown in 60% of patients, and 64% of patients with hyperphosphatemia had and incidence of grade 3 or higher [60]. In terms of quality of life, patients with stable disease

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Table 1. Clinical trial results of systemic treatments for patients with advanced BTC, including IHCCA

Line of treatment	Condition	Phase	Intervention	Primary endpoint	Patients, *n*	ORR, %	Median PFS, months	Median OS, months	Safety profile	Reference
Cytotoxic chemotherapy										
1L	BTC	3	GemCis versus gemcitabine	OS	410	26.1 versus 15.5	8.0 versus 5.0	11.7 versus 8.1	Higher neutropenia in GemCis arm	Valle et al. [8]
1L	BTC	2	GemCis versus gemcitabine	1-year OS	84	19.5 versus 11.0	5.8 versus 3.7	11.2 versus 7.7	Higher cytopenia in GemCis arm	Okusaka et al. [9]
1L	BTC	2	GEMOX	ORR	70	14.9	3.4	8.8	thrombocytopenia 14.9%	Andre et al. [12]
1L	BTC	3	GemCis versus gemcitabine + S-1	OS	354	32.4 versus 29.8	5.8 versus 6.8	13.4 versus 15.1	SAE 35.1% versus 29.9%	Morizane et al. [14]
1L	BTC	2	mFOLF IRINOX versus GemCis	6-month PFS	191	25 versus 19.4	6.2 versus 7.4	11.7 versus 13.8	SAE 72.8% versus 72.0%	Phelip et al. [16]
1L	BTC	2	GemCis + nab-paclitaxel	PFS	60	45	11.8	19.2	SAE 58%	Shroff et al. [17]
2L	BTC	3	FOLFOX versus ASC	OS	162			6.2 versus 5.3	SAE 69% versus 52%	Lamarca et al. [22]
2L	BTC	2b	nal-IRI + 5-FU versus 5-FU	PFS	174	14.8 versus 5.8	7.1 versus 1.4	8.6 versus 5.5	SAE 42% versus 24%	Yoo et al. [23]
Targeted therapy										
1L	BTC	2	Arm A: GemCis + ramucirumab Arm B: GemCis + merestinib Arm C: GemCis	PFS	309	Arm A, 31.1; arm B, 19.6; arm C, 32.7	Arm A, 6.5; arm B, 7.0; arm C, 6.6	Arm A, 10.5; arm B, 14.0; arm C, 13.0	SAE arm A, 51%; arm B, 55%; arm C, 48%	Valle et al. [76]
1L	BTC	2	GemCis versus GemCis + cediranib	PFS	124	19 versus 44	7.4 versus 8.0	11.9 versus 14.1	Higher SAE in cediranib arm, including HTN, diarrhea, cytopenia	Valle et al. [75]
1L	BTC	2	GEMOX versus GEMOX + panitumumab	PFS	89		5.3 versus 4.4	9.9 versus 10.2	Higher skin rash, diarrhea, mucositis in panitumumab arm	Leone et al. [78]
≥2L	CCA with IDH1 mutation	3	Ivosidenib versus placebo	PFS	185	2 (ivosidenib)	2.7 (ivosidenib)	10.8 (ivosidenib)		Zhu et al. [32]
≥2L	CCA with FGFR2 rearrangement	2	Infigratinib	ORR	108	23.1	7.3	12.2	Hyperphosphatemia, 76.9%; stomatitis, 54.6%; dry eye 34.3%	Javle et al. [35]
≥2L	CCA with FGFR2 rearrangement	2	Pemigatinib	ORR	107	35.5	6.9	21.1	Hyperphosphatemia, 60%; SAE, 64%	Abou-Alfa et al. [60]
≥2L	IHCCA with FGFR2 rearrangement	2	Futibatinib	ORR	103	41.7	8.9	20	Hyperphosphatemia, 85%	Goyal et al. [30]

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Table 1 (continued)

Line of treatment	Condition	Phase	Intervention	Primary endpoint	Patients, *n*	ORR, %	Median PFS, months	Median OS, months	Safety profile	Reference
≥2L	HER2-positive solid tumor	2	Pertuzumab + trastuzumab	ORR	39 (BTC)	23	4.0	10.9		Javle et al. [66]
≥2L	HER2-positive BTC	2	FOLFOX + trastuzumab	ORR	34	29.4	5.1	10.7	Grade 3–4 neutropenia 55%	Lee et al. [36]
≥2L	BRAF V600E-mutated solid tumor		Dabrafenib + trametinib	ORR	43 (BTC)	47%	9	14		Subbiah et al. [37]
≥2L	BTC	2	Regorafenib	PFS	43	11	3.6	7.3	SAE 40%	Sun et al. [38]
≥2L	BTC	2	Ramucirumab	PFS	61	1.7	3.2	9.5	HTN 22%	Lee et al. [77]
Immunotherapy										
1L	BTC	3	GemCis + durvalumab versus GemCis	OS	685	26.7 versus 18.7	7.2 versus 5.7	12.8 versus 11.5	SAE 75.7% versus 77.8%	Oh et al. [86]
1L	BTC	3	GemCis + pembrolizumab versus GemCis	OS	1,069	29 versus 29	6.5 versus 5.6	12.7 versus 10.9	SAE 85% versus, 84%	Kelley et al. [40]
1L	BTC	2	Arm A: GemCis followed by GemCis + durvalumab + tremelimumab Arm B: GemCis + durvalumab Arm C: GemCis + durvalumab + tremelimumab	ORR	128	Arm A, 50; arm B, 72; arm C, 70	Arm A, 12.8; arm B, 11.8; arm C, 12.3	Arm A, 15.0; arm B, 20.2; arm C, 18.7	Similar hematologic and non-hematologic SAE rate	Oh et al. [39]
≥2L	Solid tumor	2	Pembrolizumab		22 (CCA)	40.9 (CCA)	4.2 (CCA)	24.3 (CCA)		Marabelle et al. [41]
≥2L	BTC	2	Nivolumab	ORR	54	22	3.7	14.2	Grade 3–4 TRAE 17%	Kim et al. [42]
≥2L	BTC	1	Bintrafusp alfa	Safety	30	20	2.5	12.7	Grade 3–4 TRAE 37%	Yoo et al. [43]
≥2L	BTC	2	Arm A: atezolizumab Arm B: atezolizumab + cobimetinib	PFS	77	3.3 versus 2.8	3.7 versus 1.9		Grade 3 TRAE 38.5% versus 44.7%	Yarchoan et al. [44]

Table 1 (continued)

Line of treatment	Condition	Phase	Intervention	Primary endpoint	Patients, *n*	ORR, %	Median PFS, months	Median OS, months	Safety profile	Reference
≥2L	BTC	2	Camrelizumab + GEMOX	6-month PFS	38	54	6.1	11.8	G3 hypokalemia 19%	Chen et al. [45]
≥2L	BTC	2	Nivolumab + ipilimumab	DCR	39	23	2.9	5.7	irAE 49% (grade 3–4 in 15%)	Klein et al. [46]
1L or ≥2L	BTC	1	1L: nivolumab + GemCis 2L: nivolumab	Safety	30	37 (1L), 3 (2L)	4.2 (1L), 1.4 (2L)	15.4 (1L), 5.2 (2L)	Grade 3–4 TRAE 90% (1L), 10% (2L)	Ueno et al. [47]

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; 1L, first-line; 2L, second-line; BTC, biliary tract cancer; GemCis, gemcitabine plus cisplatin; GEMOX, gemcitabine plus oxaliplatin; mFOLFIRINOX, modified fluorouracil and leucovorin, irinotecan, and oxaliplatin; nab-paclitaxel, nano albumin bound paclitaxel; FOLFOX, fluorouracil and leucovorin plus oxaliplatin; ASC, active symptom control; nal-IRI, nanoliposomal irinotecan; SAE, serious adverse event; TRAE, treatment-related adverse event; HTN, hypertension; CCA, cholangiocarcinoma; IHCCA, intrahepatic cholangiocarcinoma; irAE, immune-related adverse event.

showed comparable outcomes to those with objective response (complete response or partial response) with maintained overall health status and improved pain and anxiety, while patients with primary progression showed deterioration in overall quality of life and symptoms associated with the disease [63]. From the exploratory biomarker analysis of the trial, the co-occurrence of alterations in *TP53*, *PBRM1*, *CDKN2A/B*, and tumor suppressor genes was significantly associated with inferior outcomes in terms of PFS [64]. Additionally, 63 genes were identified as fusion partners of the *FGFR2* gene, with *BICC1* being the most common (27.9%). There was no correlation between clinical outcomes and *FGFR2* fusion partner genes in the analysis [64].

Infigratinib, another nonselective FGFR inhibitor, also proved efficacy against previously treated *FGFR2*-rearranged advanced cholangiocarcinoma in a multicenter single-arm phase 2 trial, showing ORR of 21.3%, and median PFS and OS of 7.3 months (95% CI = 5.6–7.6) and 12.2 months (95% CI = 10.7–14.9) among 108 patients, respectively [35]. Sixty-four percent of patients experienced an adverse event of grade 3 or higher, and hyperphosphatemia of any grade was observed in 77% of patients [35]. While infigratinib and pemigatinib are ATP-competitive reversible inhibitors of *FGFR*, futibatinib is an ATP noncompetitive irreversible nonselective inhibitor of *FGFR* which showed a potential benefit regarding manageable safety profiles from a phase 1 basket trial of patients with previously treated solid tumors containing *FGF*/*FGFR* alterations [31]. In a single-arm phase 2 trial of futibatinib for patients with previously treated IHCCA containing *FGFR2* rearrangement, ORR was 41.7% with median PFS and OS of 8.9 and 20.0 months among 103 patients, respectively, with maintained quality of life through the course of treatment [30]. Currently, infigratinib and futibatinib received accelerated approval by the US FDA, and are recommended as subsequent treatment for patients with IHCCA with *FGFR2* gene rearrangement, although infigratinib is no longer available on the market as the company (Helsinn Therapeutics Inc., USA) is no longer in distribution of the product. Futibatinib also received positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) and will soon be approved by the EMA.

IDH1 Mutation

Gain-of-function mutations of the IDH1 gene are found in 13% of patients with IHCCA and are predominant in women [52, 65]. From the ClarIDHy study, a multicenter phase 3 randomized controlled trial with 185 patients with IHCCA who are refractory to prior

treatments, ivosidenib, a small molecule inhibitor of *IDH1*, showed significantly improved outcomes compared to placebo in terms of PFS with HR of 0.37 (95% CI: 0.25–0.54) and median PFS of 2.7 months and 1.4 months, respectively [65]. Ivosidenib was tolerable with comparable safety profiles with placebo group, and only 2 patients (2%) discontinued ivosidenib due to treatment-related adverse event with favorable quality-of-life assessment results [65]. With additional 1.3 years of follow-up and crossover of 43 patients (70%) in the placebo group, ivosidenib showed significantly better outcomes compared to placebo in terms of OS adjusted for crossover, with HR of 0.49 (95% 0.34–0.70) and median OS of 10.3 months and 5.1 months (adjusted), respectively [32]. Ivosidenib has been approved by the US FDA for the treatment of previously treated IHCCA patients with *IDH1* mutation. Ivosidenib also received positive opinion from the EMA's CHMP and is likely to be approved by the EMA in the near future.

HER2 Overexpression

HER2-directed therapies have shown promising outcomes in patients with BTC who progressed to prior treatments. From the report of a phase 2 MyPathway BTC cohort, which investigated the efficacy of pertuzumab plus trastuzumab in previously treated advanced BTC patients with HER2 amplification, ORR in a total of 39 patients was 23% with median PFS and OS of 4.0 months (95% CI = 1.8–5.7) and 10.9 months (95% CI = 5.2–15.6), respectively [66]. A recent multicenter phase 2 trial conducted in South Korea demonstrated a similar efficacy of trastuzumab plus FOLFOX in patients with BTC and HER2 amplification who progressed on 1 or 2 prior therapies including GemCis, with ORR of 29.4% and median PFS and OS of 5.1 months (95% CI = 3.6–6.7) and 10.7 months (95% CI = 7.9–NR), respectively [36]. However, although only a small number of patients with IHCCA were included in the trials, and the studies were not powered to compare outcomes according to primary location, patients with IHCCA showed inferior outcomes compared to the other subtypes of BTC. From the phase 2 MyPathway BTC cohort analysis, none of the 7 patients with IHCCA showed objective responses, and the median PFS and OS of the IHCCA patients were 2.6 months (95% CI = 1.0–5.3) and 3.9 months (95% CI = 1.2–8.1), respectively [66]. From the phase 2 multicenter trial of trastuzumab and FOLFOX, none of the 6 patients with IHCCA had objective responses and the median PFS and OS were 4.8 months (95% CI = 1.0–8.4) and 6.4 months (95% CI = 1.4–NR), respectively [36]. Also, the final analysis of the phase 2 SUMMIT trial BTC cohort investigating efficacy of neratinib for treatment-refractory HER2-amplified patients showed shorter survival outcomes for patients with cholangiocarcinoma compared to GBGA in terms of PFS (median: 1.4 vs. 3.7 months) and OS (median: 5.4 months and 9.8 months) [67]. Further investigations on HER2-directed treatments among HER2-amplified IHCCA patients should be performed for comparison with other subtypes of BTC, including tumor heterogeneity of HER2 overexpression.

Novel HER2-directed agents are also being investigated. Trastuzumab deruxtecan, an antibody-drug conjugate with topoisomerase I inhibitor, showed encouraging outcomes in a phase 2 trial with ORR of 36.4% and median PFS and OS of 4.4 months and 7.1 months, respectively, for patients with HER2-amplified previously treated advanced BTC [68]. Moreover, 8 patients with HER2-low expression tumors were included, and these patients showed ORR of 12.5% and median PFS and OS of 4.2 months and 8.9 months, respectively [68]. Zanidatamab is a bispecific antibody targeting the extracellular juxtamembrane domain and dimerization domain of HER2, and from the phase 1 first-in-human trial for patients with previously treated HER2-amplified solid tumor, 83 patients were in the response-evaluable population including 28% of patients with previous HER2-directed therapy, and zanidatamab monotherapy was tolerable and showed ORR of 37% [69]. Among 21 patients with BTC, objective response was observed in 8 patients (38%) and median PFS was 3.5 months (95% CI: 1.8–6.7) [69]. Currently, a phase 2b trial is ongoing to investigate its efficacy and safety for patients with previously treated HER2-amplified advanced BTC [70].

BRAF, *NTRK*, and *RET* Mutation

Several other targeted agents against genomic alterations have shown encouraging efficacy outcomes and are recommended as subsequent treatment for patients with IHCCA. Approximately 5% of patients with IHCCA have a mutation in the *BRAF* gene. In a phase 2 basket trial of dabrafenib plus trametinib, 43 patients with BTC and *BRAF* V600E mutation who progressed to prior gemcitabine-based treatment showed ORR of 47% with median PFS and OS of 9 months and 14 months, respectively [37, 51, 71]. Although rarely found, patients with *NTRK* fusion-positive IHCCA have responded to NTRK inhibitors, including entrectinib and larotrectinib

from several basket trials. It is also recommended as a subsequent treatment for patients harboring such alterations [72, 73]. Pralsetinib, a RET inhibitor, has shown activity against patients with *RET* fusion-positive IHCCA in a basket trial [74].

VEGF, *MET*, and *EGFR*

Inhibitors targeting VEGF receptor (VEGFR) have been investigated for the treatment of patients with advanced BTC, as *VEGF* and *VEGFR* genes are known to be aberrantly expressed in 40%–75% of BTC [75]. A multicenter phase 2 randomized controlled trial investigating the efficacy of adding cediranib, a VEGFR inhibitor, to GemCis compared to GemCis alone for patients with newly diagnosed advanced BTC, showed that there was no improvement in survival outcomes with the addition of cediranib to GemCis in terms of PFS (HR: 0.93, $p = 0.72$) [75]. A recent phase 2 randomized controlled trial involving ramucirumab, a monoclonal antibody against VEGFR-2, plus GemCis showed no improvement in survival outcomes for patients with newly diagnosed advanced BTC in terms of PFS (HR = 1.12, $p = 0.48$) [76]. In a phase 2 single-arm trial, the efficacy of ramucirumab in 61 patients with previously treated advanced BTC was investigated, and the median PFS and OS were 3.2 months (95% CI = 2.1–4.8) and OS of 9.5 months (95% CI = 5.8–13.6), respectively [77]. As overexpression of the *MET* gene is found in 50–60% of patients with BTC, addition of merestinib, a MET tyrosine kinase inhibitor, to GemCis was also compared with GemCis in the trial, and there was no improvement in outcomes either (HR = 0.92, $p = 0.64$) [76]. Anti-EGFR agents combined with gemcitabine-based chemotherapy regimens have been investigated as first-line treatments for advanced BTC patients, despite no significant improvement in outcomes compared to chemotherapy only [78–80]. Vandetanib, a multikinase inhibitor, as a monotherapy or combined with gemcitabine was compared with gemcitabine plus placebo as first-line treatment in a phase 2 trial including 173 patients with advanced BTC, and there was no difference in survival outcomes [81]. Regorafenib, a multikinase inhibitor, has been evaluated for efficacy in patients with previously treated advanced BTC and showed an ORR of 11% with a median PFS and OS of 15.6 weeks (90% CI = 12.9–24.7 weeks) and 31.8 weeks (90% CI = 13.3–74.3 weeks), which is comparable to cytotoxic chemotherapy regimens [38]. Table 1 summarizes the results of prospective clinical trials of targeted agents for patients with advanced BTC, including IHCCA.

Immunotherapy

The role of single-agent immunotherapy for patients with advanced cholangiocarcinoma has been evaluated in several clinical trials and showed limited efficacy outcomes with only a small proportion of patients showing durable response, including those with microsatellite instability-high (MSI-H) or deficient DNA mismatch repair (D-MMR) tumors. From the pooled analysis of the KEYNOTE-158 (regardless of PD-L1 expression) and KEYNOTE-028 trials (all patients PD-L1 positive) BTC cohort, 104 patients from the KEYNOTE-158 trial showed ORR of 5.8% with median PFS and OS of 2.0 months (95% CI = 1.9–2.1) and 7.4 months (95% CI = 5.5–9.6), respectively, while ORR was 13% for 24 patients from the KEYNOTE-028 trial, with median PFS and OS of 1.8 months (95% CI = 1.4–3.1) and 5.7 months (95% CI = 3.1–9.8) [82]. The results of safety profiles were comparable with those of other solid tumors treated with pembrolizumab, with an incidence of grade 3 or higher adverse event of 13.5% and 16.7% for the KEYNOTE-158 trial and KEYNOTE-028 trial, respectively [82, 83]. Although response rates were low, patients with objective responses showed a long duration of response, from at least 6 months to more than 4 years, indicating the need for predictive biomarkers to select suitable patients [82]. Bintrafusp Alfa, a bifunctional fusion protein designed to capture TGF-beta and block PD-L1 simultaneously, has been studied in patients with previously treated advanced BTC in a phase 1 trial. It has shown an ORR of 20% with median PFS and OS of 2.5 months (95% CI = 1.3–5.6) and 12.7 months (95% CI = 6.7–15.7), respectively [43].

PD-L1 expression in the tumor may be a potential biomarker to use to select patients for immunotherapy; however, there is limited evidence to support its use. In the phase 2 trial of nivolumab, which included 54 patients with previously treated advanced BTC, ORR was 22% with median PFS of 3.7 months (95% CI = 2.3–5.7). A subgroup analysis comparing median PFS according to PD-L1 expression showed prolonged survival for patients with PD-L1 positive, defined as ≥ 1% tumor cells with membranous staining of PD-L1 by immunohistochemistry with any intensity (median PFS: 10.4 vs. 2.3 months, HR = 0.23, $p < 0.001$) [42]. In contrast, a pooled analysis of the KEYNOTE-158 and KEYNOTE-028 trials showed a numerically higher ORR in patients with PD-L1-positive IHCCA but no difference in outcomes in terms of PFS and OS [82]. Patients with MSI-H/D-MMR IHCCA have shown promising outcomes from KEYNOTE-158 non-colorectal MSI-H/D-MMR cohort results in 9 of 22 patients (40.9%),

showing objective response to pembrolizumab, and median PFS and OS were 4.2 months (95% CI = 2.1–NR) and 24.3 months (95% CI = 6.5–NR), respectively [41]. However, MSI-H/D-MMR IHCCA is known to account for only 2% of BTC patients, and there are still unmet needs for additional biomarkers [84].

Combination regimens of immunotherapy have also been investigated for the treatment of patients with previously treated IHCCA. Sub-analysis results from the multicenter phase 2 basket trial of nivolumab plus ipilimumab combination for previously treated rare solid tumors (39 patients with BTC) have shown ORR of 23% with median PFS and OS of 2.9 months (95% CI = 2.2–4.6) and 5.7 months (95% CI = 2.7–11.9), respectively [46]. Patients received four cycles of nivolumab plus ipilimumab followed by nivolumab maintenance. Immune-related adverse events were experienced in 49% of patients, including 15% of patients with adverse events of grade 3 or higher [46]. In a randomized phase 2 trial evaluating the efficacy of atezolizumab with or without cobimetinib (a MEK inhibitor), 77 patients with previously treated advanced BTC received treatment with a modest survival benefit of combination treatment compared to atezolizumab monotherapy in terms of PFS (median: 3.7 vs. 1.9 months, HR = 0.58, $p = 0.027$). There was a higher incidence of grade 3 or higher adverse events among combination arm (44.7% vs. 38.5%) [44]. A combination of pembrolizumab with capecitabine and oxaliplatin for patients with previously treated advanced BTC was evaluated in a phase 2 trial with 11 patients. It showed ORR of 27.3% with median PFS of 4.1 months [85].

The role of immunotherapy in first-line setting for the treatment of patients with advanced BTC has recently been investigated. A phase 1 trial investigating the role of nivolumab for the treatment of advanced BTC patients in 30 patients who received nivolumab plus GemCis as first-line treatment showed ORR of 36.3% and median PFS and OS of 4.2 months (90% CI = 2.8–5.6) and 15.4 months (95% CI = 11.8–NR); however, further randomized trials are needed to prove the benefit of nivolumab combination in first-line setting [47]. Another single-arm phase 2 trial of GEMOX with camrelizumab in 38 patients with newly diagnosed advanced BTC showed no improvement when immunotherapy was combined with chemotherapy compared to historic cohorts with median PFS and OS of 6.1 months and 11.8 months, respectively [45]. A single-center phase 2 trial in South Korea investigated the role of PD-L1 blockade plus chemotherapy with or without additional CTLA-4 inhibition for the first-line treatment of advanced BTC [39]. With a total of 128 enrolled, patients received either GemCis followed by GemCis plus durvalumab and tremelimumab, GemCis plus durvalumab, or GemCis plus durvalumab and tremelimumab. There was no significant improvement in outcomes with the addition of tremelimumab [39].

Subsequently, a phase 3 TOPAZ-1 trial comparing outcomes of advanced BTC patients treated with durvalumab plus GemCis and GemCis was conducted, and with 685 patients randomly assigned, the addition of durvalumab to GemCis significantly improved outcomes in terms of OS (median: 12.8 vs. 11.5 months, HR = 0.80, $p = 0.021$, 2-year OS rate: 24.9% vs. 10.4%) with comparable safety outcomes (grade 3–4 adverse event, 75.7% vs. 77.8%), and has been approved as first-line treatment [86]. With addition of 6 months of follow-up, durvalumab plus GemCis maintained significant OS benefit (HR: 0.76 [95% CI: 0.64–0.91]) with median OS of 12.9 months compared to 11.3 months for GemCis plus placebo group [87]. Immune-mediated adverse event was found in 12.7% of patients who received additional durvalumab, including 2.4% of patients with grade 3–4 event, and 0.9% of patients discontinuing the treatment due to adverse events [88]. In the quality-of-life investigation, there was no difference between the GemCis group and durvalumab plus GemCis group [89]. From the exploratory analysis, the efficacy and safety outcomes were similar across different regions (Asia vs. others) and primary tumor location (IHCCA vs. EHCCA vs. GBCA) [90, 91]. From biomarker analysis, although patients with actionable alterations (*IDH1* mutation, *FGFR2* rearrangement, and *BRAF* mutation) showed HR of less than 1 for durvalumab plus GemCis in terms of OS, there was no statistical significance due to small sample size, and patients with *ERBB2* amplification had HR for OS of 1.71 (95% CI: 0.82–3.56) [92]. Among patients treated with durvalumab plus GemCis, there was no negative association between OS outcomes with antibiotics usage during the treatment [93]. In the exploratory analysis of the TOPAZ-1 trial, proportion of long-term survivors, defined as patients who survived ≥18 months from randomization, was higher in the durvalumab plus GemCis group compared to the GemCis group, although the difference was minimal (20.4% vs. 18.9%) [94]. Patients with long-term survival tended to have recurrent disease than initially metastatic disease in both durvalumab plus GemCis and GemCis group [94].

Another global phase 3 trial has proven clinical benefit of adding immunotherapy to GemCis as first-line treatment for previously untreated advanced BTC patients [40]. In the phase 3 KEYNOTE-966 trial, patients treated with pembrolizumab plus GemCis showed significantly

Table 2. Ongoing clinical trials on advanced IHCCA and BTC

Clinicaltrials.gov ID	Conditions	Intervention	Setting	Phase	Completion date
Cytotoxic chemotherapy					
NCT03768414	BTC	Nab-paclitaxel + GemCis versus GemCis	First-line	Phase 3	2024.1.1
NCT04692051	BTC	Nab-paclitaxel + cisplatin versus GemCis	First-line	Phase 2	2021.9.1
NCT04059562	CCA	Trifluridine/tipiracil + irinotecan	Second-line	Phase 2	2024.4.1
NCT04111380	BTC	Nab-paclitaxel + cisplatin	Second-line or higher	Phase 2	2023.9.1
Targeted therapy					
NCT03656536	CCA with FGFR2 rearrangement	Pemigatinib versus GemCis	First-line	Phase 3	2028.7.27
NCT04042831	BTC with platinum response and DDR pathway alteration	Olaparib	First-line or maintenance after first-line	Phase 2	2024.9.30
NCT04521686	Solid tumor with IDH1 or IDH2 mutation	LY3410738 (IDH inhibitor)	First or subsequent	Phase 1	2023.5.1
NCT04466891	BTC with HER2 positive	Zanidatamab	Second-line or higher	Phase 2	2024.6
NCT04526106	Solid tumor with FGFR2 rearrangement	RLY-4008 (selective FGFR2 inhibitor)	Second-line or higher	Phase 1/2	2024.10.1
NCT05190575	BTC with claudin 18.2 positive	TST001 (claudin 18.2 mAb)	Second-line or higher	Phase 2	2024.7.30
NCT04353375	IHCCA with FGFR2 rearrangement	HMPL-453 (FGFR 1–3 inhibitor)	Second-line or higher	Phase 2	2023.6.30
NCT03110484	BTC	Pemetrexed + erlotinib	Second-line or higher	Phase 2	2024.6.14
NCT05170438	BTC	Lenvatinib + paclitaxel	Second-line or higher	Phase 2	2028.6.30
Immunotherapy					
NCT03260712	BTC	Pembrolizumab + GemCis	First-line	Phase 2	2023.6.1
NCT04003636	BTC	Pembrolizumab + GemCis versus GemCis	First-line	Phase 3	2023.8.31
NCT04677504	BTC	Atezolizumab + GemCis versus atezolizumab + bevacizumab + GemCis	First-line	Phase 2	2023.4.24
NCT04066491	BTC	Bintrafusp alfa + GemCis versus GemCis	First-line	Phase 3	2022.12.31
NCT05342194	IHCCA	Toripalimab with or without lenvatinib + GEMOX or GemCis versus GEMOX or GemCis	First-line	Phase 3	2027.5.31
NCT04910386	BTC	Envafolimab + GemCis versus GemCis	First-line	Phase 2	2027.6.1
NCT05222971	BTC with response to platinum and DDR pathway alteration	Olaparib or olaparib + durvalumab	Maintenance after first-line	Phase 2	2024.10.30
NCT03639935	BTC	Nivolumab + rucaparib	Maintenance after first-line	Phase 2	2024.1.1
NCT05510427	CCA with FGFR2 rearrangement	Infigratinib + atezolizumab + bevacizumab	Second-line	Phase 1	2023.11.19

Table 2 (continued)

Clinicaltrials.gov ID	Conditions	Intervention	Setting	Phase	Completion date
NCT04211168	BTC	Toripalimab + lenvatinib	Second-line	Phase 2	2022.12.1
NCT04298021	BTC	AZD6738 + durvalumab or AZD6738 + olaparib	Second-line	Phase 2	2022.3.31
NCT05174650	IHCCA with FGFR2 rearrangement	Atezolizumab + derazantinib	Second-line or higher	Phase 2	2026.8.1
NCT03633773	IHCCA	MUC-1 CAR-T cell	Second-line or higher	Phase 1/2	2024.12.31
NCT04941287	BTC	Atezolizumab + varlilumab with or without cobimetinib	Second-line or higher	Phase 2	2023.9.1
NCT04727996	BTC	Tislelizumab + sitravatinib	Second-line or higher	Phase 2	2022.10.31
NCT05052099	BTC	Atezolizumab + bevacizumab + mFOLFOX6	Second-line or higher	Phase 1/2	2024.6.1
NCT04550624	BTC	Pembrolizumab + lenvatinib	Second-line or higher	Phase 2	2025.12.1
NCT03801083	BTC	Lymphodepletion and autologous TIL infusion followed by IL-2	Second-line or higher	Phase 2	2025.1.1

BTC, biliary tract cancer; nab-paclitaxel, nano albumin bound paclitaxel; GemCis, gemcitabine plus cisplatin; CCA, cholangiocarcinoma; DDR, DNA damage repair; mAb, monoclonal antibody; GEMOX, gemcitabine plus oxaliplatin; IHCCA, intrahepatic cholangiocarcinoma; CAR-T, chimeric antigen receptor-T cell; mFOLFOX, modified fluorouracil and leucovorin plus oxaliplatin; TIL, tumor-infiltrating lymphocyte; IL-2, interleukin-2.

better OS outcomes compared to those treated with GemCis (median OS: 12.7 vs. 10.9 months, HR: 0.83, $p = 0.0034$), and in the subgroup analysis, IHCCA showed significant interaction favoring additional pembrolizumab [40]. However, considering the modest improvement in OS of patients treated with immunotherapy plus GemCis arm compared to GemCis alone and the cost of treatment, further studies are needed to define predictive biomarkers to select optimal patients for immunotherapy [40, 86]. Table 1 summarizes prospective clinical trial results of immunotherapies for patients with advanced BTC, including IHCCA.

Future Directions

Despite the recent improvement of clinical outcomes in patients with advanced IHCCA with new therapeutic options, most patients eventually develop resistance to the treatment, and progression of the tumor occurs within a year. Indeed, there should be further efforts to improve the outcomes of patients with advanced IHCCA. For patients with actionable genomic alterations, targeted agents have shown encouraging efficacy outcomes, and precise genomic profiling is essential to provide optimal treatment. However, it is often challenging to obtain adequate tumor sample for next-generation sequencing in patients with cholangiocarcinoma. Further investigation to utilize genomic profiling through plasma circulating tumor DNA for the detection of actionable alterations should be performed and compared with matched tumor genomic profiling to evaluate sensitivity and specificity of the methods in patients with advanced IHCCA. Serial monitoring of genomic profiles with plasma circulating tumor DNA sequencing may improve clinician knowledge regarding resistance clone development. More real-world evidence of efficacy and safety profiles of the targeted agents is needed to evaluate the role of the agents and the prognosis of patients with certain genomic alterations. Also, further studies of genomic profiles of IHCCA should be performed to discover prognostic/predictive biomarkers of currently used agents and potential therapeutic targets. The application of targeted agents in combination with other cytotoxic agents or immunotherapy, or the use of targeted agents in the first-line setting should be investigated, and phase 3 trials comparing GemCis and pemigatinib (NCT03656536) are ongoing for the first-line treatment of advanced BTC with *FGFR2* rearrangement. Table 2 shows ongoing clinical trials of targeted agents for the treatment of patients with advanced IHCCA.

Patients treated with targeted agents eventually develop acquired resistance. The biomarker analysis of the FIGHT-202 trial, which is a genomic profiling of 8 patients who progressed after response to pemigatinib, showed at least one acquired mutation in the *FGFR2* kinase domain after progression, which is known to cause resistance to FGFR inhibitors [64]. A single-center exploratory analysis of 4 patients who received futibatinib after progression to infigratinib or pemigatinib showed that futibatinib, which is an irreversible FGFR inhibitor, may overcome acquired resistance mutations of the *FGFR2* kinase domain, although mutation at the V565 gatekeeper site remained resistant to all FGFR inhibitors, including futibatinib [34]. Also, patients with *IDH1* mutation who were treated with ivosidenib eventually developed acquired resistance. From a genomic profiling analysis of 2 patients with *IDH1* R132C-mutated IHCCA who progressed to ivosidenib treatment, 1 patient developed de novo *IDH1* D279N mutation. From in vitro analysis, cells harboring both *IDH1* R132C and D279N mutations which maintained the capability of producing 2-HG under ivosidenib, the *IDH1* function was blocked by LY3410738, an irreversible IDH1 inhibitor [95]. Further studies should be performed to investigate the resistance mechanism of ivosidenib and how to overcome it, including LY3410738 which has shown preclinical evidence to overcome acquired resistance.

Efforts to identify predictive biomarkers in patients with IHCCA are warranted to optimize the outcomes of patients treated with immunotherapy. The tumor microenvironment of cholangiocarcinoma is characterized by dense fibrous stroma enriched with cancer-associated fibroblasts which may hinder infiltration of effector phenotype $CD8^+$ T cells, and eventually explain the low response rate of immune checkpoint inhibitors [96–98]. Indeed, further studies to improve understanding of the tumor microenvironment of cholangiocarcinoma and to discover potential targets to turn the tumor into "hot tumor" should be performed. Combining immunotherapy with other cytotoxic agents or targeted agents may improve the efficacy of the treatment. The phase 2 IMbrave151 trial, which compares atezolizumab with or without bevacizumab plus GemCis as first-line treatment for patients with advanced BTC, is ongoing (NCT04677504). From a genomic profiling analysis of 88 patients with advanced BTC, 55 patients (63.5%) who had alterations in the DNA damage repair pathway, including *BRCA2*, *ATM*, *ATR*, *BRIP1*, and *MLH1*, showed significantly better survival outcomes to first-line platinum doublet chemotherapy [99]. A phase 2 trial of durvalumab with or without olaparib, a poly-ADP ribose polymerase inhibitor, is ongoing for advanced BTC patients with alterations in the DNA damage repair pathway who showed durable response to a first-line platinum-containing regimen (NCT05222971). Adoptive cell therapy is another treatment modality with a potential role in the treatment of patients with advanced cholangiocarcinoma. A report of a patient with advanced refractory BTC treated with autologous $CD4^+$ Th1 tumor-infiltrating lymphocyte recognizing the mutated ERBB2 interacting protein of the tumor showed durable response with substantial regression of the tumor [100]. Table 2 shows ongoing trials of immunotherapy for patients with advanced IHCCA.

For patients with locally advanced unresectable IHCCA, the addition of locoregional modalities has been shown to improve outcomes in several studies. From a retrospective analysis of 79 patients with locally advanced unresectable IHCCA who received radiotherapy in addition to systemic chemotherapy, the median OS was 30 months. This is numerically longer than the outcomes of the post hoc analysis of liver-only IHCCA patients from ABC-01, 02, 03 trials, which showed a median OS of 16.7 months (95% CI = 8.7–20.2) [101, 102]. From the analysis, patients receiving a biologically equivalent dose higher than 80.5 Gy showed a significantly higher 3-year OS rate compared to those who received less than 80.5 Gy (73% vs. 38%, $p = 0.017$). There were no significant treatment-related toxicities reported [101]. In a single-center retrospective analysis of 104 patients with locally advanced unresectable IHCCA treated with systemic chemotherapy with or without hepatic arterial cytotoxic agent infusion, patients treated with systemic treatment with hepatic arterial infusion showed significantly better OS compared to systemic treatment alone in patients with disease confined to the liver (median OS: 30.8 vs. 18.4 months, $p < 0.001$) [103]. Also, a significant survival benefit of adding hepatic arterial infusion to systemic treatment was observed in patients with locoregional lymph node metastasis with median OS of 29.6 months and 15.9 months, respectively ($p < 0.001$) [103].

Prospective clinical trials may be performed to evaluate the role of radiotherapy or hepatic arterial infusion in patients with locally advanced unresectable IHCCA. *Trans*-hepatic radioembolization with yttrium-90 microspheres combined with concurrent GemCis for the treatment of patients with unresectable IHCCA has been evaluated in a European phase 2 clinical trial of 41 patients. The ORR was 39% with median PFS and OS was 14 months (95% CI = 8–17) and 22 months (95% CI = 14–52) [104]. Although 29 patients (71%) experienced grades 3–4 adverse events, 9 patients (22%) achieved resectability following the treatment and received R0 surgical resection with median 2-year OS rate from the

surgery of 88.9% among those who had surgery [104]. The combination of yttrium-90 microspheres and GemCis chemotherapy was also evaluated in a multicenter study in Asia. In this phase 2 study, patients with locally advanced IHCCA were treated with one cycle of yttrium-90 followed by GemCis chemotherapy if they were fit. The study reported a response rate of 25% and a disease control rate of 75%. The median OS was 13.6 months in the intention-to-treat population (i.e., yttrium-90 with or without chemotherapy), but the median OS was 21.6 months in patients who completed both yttrium-90 and chemotherapy. In contrast to the aforementioned clinical trial, grade 3–4 treatment-related adverse events occur in less than 10% of patients. There is likely heterogeneity in the patient population in the Asian and European clinical trials, leading to differences in efficacy and toxicity. However, both clinical trials consistently suggested a synergism between yttrium-90 and chemotherapy. Further studies are necessary to clarify the patient selection strategy [105].

Conclusion

Recent advances in systemic treatments have improved clinical outcomes of patients with advanced IHCCA. The addition of durvalumab to the GemCis regimen has significantly improved OS and is currently recommended as one of the standard first-line treatment options. Also, nab-paclitaxel plus GemCis as first-line treatment for advanced BTC patients has shown promising survival outcomes in a phase 2 trial. The ABC-06 and NIFTY trials have proven beneficial as second-line doublet cytotoxic chemotherapy and have provided a treatment option for patients without actionable alterations who progressed to first-line therapy. For patients with actionable genomic alterations, including *FGFR2* rearrangement, *IDH1* mutation, *BRAF* mutation, and *ERBB2* amplification, targeted agents are recommended as subsequent treatments. Immune checkpoint inhibitors are being investigated for the treatment of previously treated patients, although only a small proportion of patients showed durable responses.

Conflict of Interest Statement

Changhoon Yoo received honoraria from Servier, Bayer, AstraZeneca, Merck Sharp & Dohme, Eisai, Celgene, Bristol Myers Squibb, Debiopharm, Ipsen, Kyowa Kirin, Novartis, Boryung Pharmaceuticals, Merck Serono, Mundipharma, Roche, and Janssen, and received research grants from Servier, Bayer, AstraZeneca, Ono Pharmaceuticals, Celgene, Ipsen, Boryung Pharmaceuticals, Ildong Pharmaceuticals, CKD Pharmaceuticals, and HK inno.N. Stephen L. Chan received research grant from the SIRTEX, MSD, Ipsen, and AstraZeneca; have advisory role in AstraZeneca, MSD, and Eisai.

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